Docket No. 17620.105003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Fumitoshi Asai et al.	Confirmation No. :	7488
Serial No.:	10/600,266	Group Art Unit:	1629
Filed:	June 20, 2003	Examiner:	Leslie A. Royds Draper
For:	Medicinal Compositions Containing Aspirin		

SUPPLEMENT STATEMENT TO THE IDS FILED UNDER 37 C.F.R. § 1.97

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir or Madam:

Applicants respectfully request consideration of additional information concerning the recent publication of the results of the TRILOGY ACS study published in Roe et al., "Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization," The New England Journal of Medicine, August 26, 2012 at NEJM.org. The results were also presented at the ESC ("European Society of Cardiology") Congress in Munich, Germany. A joint press release by Daiichi Sankyo Company, Ltd., and Eli Lilly and Company summarized the results. All of the above are submitted herewith this Supplemental Statement to the IDS Filed Under 37 C.F.R § 1.97.

REMARKS

I. STATUS OF THE CLAIMS

The status of the claims has not changed since the submission of Applicants' response of July18, 2012.

II. TRILOGY ACS

On August 26, 2012, Daiichi Sankyo Company, Limited and Eli Lilly and Company published the results of The Targeted Platelet Inhibition to Clarify the Optimal Strategy Medically Manage Acute Coronary Syndromes ("TRILOGY ACS") study in The New England Journal of Medicine. The study reports the results of a phase III trial comparing the administration of a combination of prasugrel and aspirin to clopidogrel and aspirin in patients treated for unstable angina or myocardial infarction without ST-segment elevation who do not undergo revascularization. Patients were treated for 30 months.

The data generated in the TRILOGY ACS study reveal that the combination of prasugrel and aspirin provides an unexpected benefit to several population groups, for example patients with multiple recurrent ischemic events; current or recent smokers; patients who underwent angiography prior to randomization; and patients taking a proton pump inhibitor at randomization. In addition, the data revealed a continuing divergence after twelve months between the patients treated with prasugrel and aspirin and those treated with clopidogrel and aspirin such that those treated with prasugrel and aspirin have a reduced risk of death as a result of cardiovascular causes, all myocardial infarctions, and stroke. However, if one only considers the data at the median point of 17 months, the time chosen for evaluating the primary end point of the study, the primary end point of "death from cardiovascular causes, myocardial infarction, or stroke among patients under the age of 75 years occurred in 13.9% of the prasugrel group and 16.0% of the clopidogrel group (hazard ratio in the prasugrel group, 0.91; 95% confidence

interval [CI], 0.79 to 1.05; P=0.21)...." Based on these results of the primary end point at 17 months, the study concludes that "[a]mong patients with unstable angina or myocardial infarction without ST-segment elevation, prasugrel did not significantly reduce the frequency of the primary endpoint, as compared with clopidogrel, and similar bleeding risks were observed." As explained more fully below, this conclusion regarding the primary end point contrasts with several unexpected beneficial effects.

Applicants bring the publications related to the TRILOGY ACS trial to the Examiner's attention because they provide additional information related to comments made by the Examiner in the Office Action dated March 30, 2012 and to which Applicants' responded on July 18, 2012. In the Office Action of March 30, 2012, the Examiner asserted that much of the data relied on by Applicants had resulted from the earlier TRITON study involving patients with acute coronary syndrome undergoing percutaneous coronary intervention. Applicants responded by discussing the appropriate legal framework for considering the data previously presented by Applicants and the broader relevance of the data.

The results of the TRILOGY ACS study further demonstrate the unexpected benefits provided by the combination prasugrel and aspirin. As shown in Figure 2 of the Roe et al., NEJM TRILOGY ACS report, there is a clear trend among several subpopulations of patients involved in the study that demonstrate an apparent benefit of prasugrel and aspirin compared to clopidogrel and aspirin. Besides an overall trend favoring prasugrel, statistically significant benefits of prasugrel and aspirin over clopidogrel and aspirin were identified in certain subgroups of populations. Specific subgroups that demonstrated an apparent positive interaction with prasugrel and aspirin that was not time dependent were current and recent smokers

(P<0.001), those who underwent angiography before randomization (P=0.08), and those taking a proton-pump inhibitor at randomization (P=0.02). See, Fig. 2.

The divergence between prasugrel and aspirin and clopidogrel and aspirin observed after twelve months provides further evidence of the unexpected and beneficial properties provided by the claimed invention of prasugrel and aspirin. As stated by Roe et al.,

> An unexpected time-dependent divergence of treatment effect was observed after 12 months of therapy among patients under the age of 75 years. When evaluated before and after 12 months, the interaction of the treatment effect of prasugrel for the time to the first event was week, but the late separation of the event curves was consistent for both primary and component end points, an observation that was also apparent in the analysis of multiple recurrent ischemic events.

Roe et al., NEJM at 9. This trend is evident in Figure 1, in which separation between the prasugrel and clopidogrel curves begins after about a year of treatment and continues thereafter. The divergence between co-administration of prasugrel and aspirin and clopidogrel and aspirin was observed and reported for each of the secondary end points: death from cardiovascular causes, all myocardial infarctions, and strokes.

Further analysis of the time divergence effects regarding the frequency of the primary end point among patients under the age of 75 years revealed similar results among study groups for the first 12 months. After the 12 month period, however, a difference between the prasugrel and clopidogrel groups was observed. See Fig. 1A. As stated by Roe et al.,

> Hazard ratios and 95% confidence intervals for the time period of 12 months or less versus the time period of more than 12 months comparing prasugrel with clopidogrel for the primary efficacy end point were 0.99 (95% CI, 0.84 to 1.16) versus 0.72 (95% CI, 0.54 to 0.97) (p=0.07 for interaction).

Roe et al., NEJM at 7.

Another group of patients that benefits more from the prasugrel and aspirin combination than the clopidogrel and aspirin combination are those patients who have multiple recurrent

ischemic events. P=0.04. Id. at 6. When this group was further analyzed using the 12 month time point, there was an even greater level of significance for the prasugrel/aspirin treatment (P=0.02).

> The prespecified analysis that was performed to account for multiple recurrent ischemic events suggested a lower risk among patients under the age of 75 years in the prasugrel group (hazard ratio, 0.85; 95% CI, 0.72 to 1.00; p=0.04). Among patients who had an ischemic event, 364 patients in the prasugrel group (10.1%) had at least one ischemic event, as compared with 397 patients in the clopidogrel group (11.0%), whereas 77 (2.1%) versus 109 (3.0%) had at least two recurrent ischemic events, and 18 (0.5%) versus 24 (0.7%) had at least three recurrent ischemic events, respectively.
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> In the time-dependent analysis of recurrent events using a 12-month landmark time point, there was a significant interaction with treatment and time (p=0.02). The risk of recurrent ischemic events in the prasugrel group was lower after 12 months (hazard ratio for <12 months, 0.94 [95% CI, 0.79 to 1.12], vs. hazard ratio for ≥12 months, 0.64 [95% CI, 0.48 to 0.86]).

See Roe et al., NEJM at 6 and 9.

Applicants have provided considerable amounts of evidence to demonstrate the unexpected and beneficial properties of prasugrel and aspirin combinations. These properties are numerous and provide distinct and measurable advantages over clopidogrel and aspirin. Moreover, these advantages are observed despite prasugrel's greater tendency to cause increases in bleeding, which in the TRILOGY ACS study continued to be a cause for concern and monitoring.

The TRITON study demonstrates statistically beneficial effects of administering prasugrel and aspirin to patients undergoing percutaneous coronary intervention ("PCI") for patients with acute coronary syndromes. Such intervention is the recommended course of treatment for patients with acute coronary syndromes consisting of unstable angina or myocardial infarction without ST-segment elevation. Although such intervention is recommended, a large number of patients are treated medically without PCI which is used to

cause revascularization. The TRILOGY ACS study looked at the population of such patients treated medically without PCI and found a clear benefit of prasugrel/aspirin for certain sub-populations and a trend for the larger group, which did not meet the 0.05% level of significance at 17 months for the primary end point. The trend in favor of prasugrel/aspirin and increase in separation of effects over time, particularly after 12 months, led the authors of the TRILOGY ACS study to suggest that "it is possible that a median follow-up period of 17 months was not long enough to explore the divergence of ischemic events in patients receiving medical therapy alone." Id. at 9.

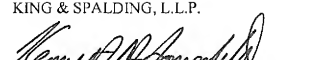
The combination of the TRITON and TRILOGY ACS studies provides a large amount of data supporting the unexpected benefits of prasugrel/aspirin treatments for patients with acute coronary syndromes without unacceptable bleeding risks. The clear benefit for patients having undergone PCI may be related to such patients being at greater risk either due to increased vascular injury and consequence of platelet aggregation, or the PCI and stent placement procedures themselves that may amplify platelet reactivity. The greater platelet inhibition of prasugrel compared to clopidogrel may therefore be more apparent in patients in the TRITON study, than those selected for the TRILOGY ACS study who were only treated medically without PCI. Both studies, however, provide important data that identifies large populations of individuals for whom the combination of prasugrel and aspirin provided unexpected and life saving benefits compared to clopidogrel and aspirin, without unacceptable bleeding risks.

Applicants respectfully requests that the Examiner considers the additional information which, when considered as whole, and in combination with the other information already provided to the Examiner, further supports the unexpected results of prasugrel and aspirin and the patentability of Applicants' pending claims.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees which may be required for consideration of this paper to Deposit Account No. **50-3732**, Order No. 17620.105003. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 17620.105003.

Respectfully submitted,
KING & SPALDING, L.L.P.

Dated: September 7, 2012 By: 
Kenneth H. Sonnenfeld
Registration No. 33,285

Correspondence Address:
King & Spalding LLP
1185 Avenue of the Americas
(212) 556 - 2100 Telephone
(212) 556 - 2222 Facsimile